

(2) fibrotic growth factors, such as TGF $\beta$ -1, TGF $\beta$ -2, PDGF, and mixtures of two or more thereof, wherein the fibrotic growth factors are present in a lower proportion than the non-fibrotic growth factor compared to the growth factors present naturally in wounds or disorders in question, or (3) with such fibrotic growth factors together with anti-fibrotic agents against them. These agents are incorporated into a pharmaceutically acceptable carrier.

Applicants have discovered a means to promote healing by using non-fibrotic growth factors or fragments to overcome scarring which would normally occur. Certain claims are directed to specific growth factors, such as TGF $\beta$ -3 and FGF.

At page 8 through page 15, Applicants have included experimental data showing tests using TGF $\beta$ -1, TGF $\beta$ -2 or TGF $\beta$ -3. Additionally, tests were run where antibodies for neutralizing TGF $\beta$ -1 (anti-TGF $\beta$ -1) and TGF $\beta$ -2 (anti-TGF $\beta$ -2) were used.

In tests, wounds treated with TGF $\beta$ -3, anti-TGF $\beta$ -1 and anti-TGF $\beta$ -2 have less fibronectin and better orientation, than wounds treated with TGF $\beta$ -1 or TGF $\beta$ -2 which have increased fibronectin with abnormal orientation. Additionally, wounds treated with TGF $\beta$ -3 contained a low profile of macrophages, while wounds treated with TGF $\beta$ -1 and TGF $\beta$ -2 contained a higher profile of macrophages. TGF $\beta$ -3 treated wounds develop more blood vessels compared to the control wounds or wounds treated with TGF $\beta$ -1 or TGF $\beta$ -2. Applicants note that this is a marked effect. TGF $\beta$ -3 and anti-TGF $\beta$ -1 and TGF $\beta$ -2 treated wounds have collagen having a similar reticular pattern to the surrounding dermis, while TGF $\beta$ -1 and TGF $\beta$ -2 treated wounds and the control wounds have abnormal orientation of collagen.

As the data shows,  $TGF\beta$ -3, unlike  $TGF\beta$ -1 or  $TGF\beta$ -2, acts to reduce wound scarring. Additionally, using anti-  $TGF\beta$ -1 and anti- $TGF\beta$ -2 improves wound healing by reducing scarring.

**Rejections under 35 U.S.C. §102(b)**

Applicants acknowledge the withdrawal of the rejection based on Ruoslahti et al (WO 91/10727).

Claims 1, 3, 6, 17 and 18 stand rejected under 35 U.S.C. §102(b) as being anticipated by the PCT publication WO 90/03810 (hereafter Geistlick et al). The rejection states that Geistlick et al teach delayed release compositions for wound healing. The compositions are then dispersed in a hydrogel. The rejection states that mere recitation of newly discovered functional properties, inherently possessed by a composition, does not cause a claim to be distinguished over the prior art.

Geistlick et al relate to delayed release agents for wound healing. Geistlick et al do not teach or suggest the use of the specific combinations of agents required by Applicants' claims. Applicants' claim non-fibrotic growth factors used without fibrotic growth factors or with specific combinations of other components. Geistlick et al only teach generalized use of "growth factors" and does not contain any teachings to Applicants' claimed limitations. Specifically, Applicants' claims require a non-fibrotic growth factor, which is not disclosed or taught by Geistlick et al, with no fibrotic growth factor or in combination with specific materials. Geistlick et al do not contain any teachings to any specific non-fibrotic growth factors together with (1) no fibrotic

growth factor, (2) fibrotic growth factors at lower concentration that occur naturally, and (3) fibrotic growth factor together with anti-fibrotic agents. Without teaching or suggesting the specific limitations of Applicants' claims, Geistlick et al cannot anticipate their claims.

The Office Action indicates that Geistlick et al teach a hydrogel containing one or more gelable proteins. The gelable proteins are considered to include one or more growth factors. However, there is no teaching in Geistlick et al to the specific requirements of Applicants' claims. The Office Action indicates the mere recitation of newly discovered function or property is inherently possessed by the prior art. However, Applicants are not claiming the same composition having a new function. Applicants' claimed composition are different from those that are naturally occurring, such as those in Geistlick et al. Applicants are not just claiming a new function, but are claiming a new composition and therefore, submit that Geistlick et al do not anticipate their claims. Since Geistlick et al do not teach or suggest each element of Applicants' claims, Applicants submit that Geistlick et al do not anticipate their claims. Accordingly, Applicants request withdrawal of the rejection.

Claims 1, 2, 6, 7, 12 and 14-20 stand rejected under 35 U.S.C. §102(b) as anticipated by Cerlitti et al. The rejection states that Cerlitti et al teach a method for treating wounds with TGF  $\beta$  like proteins. The rejection notes that Cerlitti et al teaches TGF $\beta$ -1, TGF $\beta$ -2 and TGF $\beta$ -3. The rejection states that the TGF $\beta$  proteins of Cerlitti et al would inherently possess the properties of the compositions of Applicants' claims.

Cerlitti et al relate to a process for producing biologically active, dimeric TGF- $\beta$  compositions and pharmaceutical compositions comprising the compositions. Cerlitti et al do not teach the use of TGF $\beta$ -3 in the specific compositions required by Applicants' claims. Applicants are not claiming a new use for an old compound, but are claiming non-fibrotic growth factors in specific compositions which are different from those that occur naturally. Cerlitti et al disclose many processes for preparing TGF $\beta$  proteins. However, there is no teaching or suggestion that shows that the resulting proteins are Applicants' claimed combination. Applicants have specifically structured their claims so that the non-fibrotic growth factor is used with no fibrotic growth factor or in combination with other materials to bring about a composition which is particularly effective in wound healing without scarring. Cerlitti et al do not teach or suggest such combination. Cerlitti et al do not teach or suggest a difference between the different TGF $\beta$  proteins. Without teachings of the specific claimed combinations, Cerlitti et al cannot anticipate Applicants' claims. Accordingly, Applicants request withdrawal of this rejection.

The rejection states that the compositions of the prior art references inherently possess the function of Applicants' claimed combination. However, as discussed above, there are specific elements of Applicants' claims which are missing from the prior art references. Even if the compositions of Geistlick et al and Cerlitti et al possessed beneficial wound healing properties, the compositions would not anticipate Applicants' claims because of the lack of required claimed elements. Additionally, neither reference suggests Applicants' claimed compositions. The references are

devoid of any teachings to the benefits of non-fibrotic growth factors without fibrotic growth factors or with fibrotic growth factors present in lower amounts than occur naturally or with fibrotic growth factors with anti-fibrotic agents in wound healing compositions. There is no teachings within the references or reason of record that would lead one of ordinary skill in the art toward Applicants' claimed combination. Additionally, within the specification, Applicant has submitted test data, discussed above, which reveals the unexpected benefit of the Applicants' claimed compositions in wound healing. Accordingly, withdrawal of the rejections based on these references is respectfully requested.

#### **35 U.S.C. § 112 Rejections**

The specification is objected to and claims 4 and 5 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide adequate written support. Specifically, the use of the term "anti-fibrotic agents" is questioned.

At page 15, second paragraph, Applicants define anti-fibrotic agents as being anti-scarring agents. Page 1, paragraph 2, defines fibrosis. Anti-fibrotic agents may be defined as agents which promote reduced fibrosis. An example of an anti-fibrotic agent is an agent which inhibits scarring during wound healing. Applicants have taught what determines an anti-fibrotic agent. Applicants are entitled to use the term provided a skilled person would be enabled to make and use Applicants' invention. Applicants have provided ample description including specific examples of the anti-fibrotic agent for a person of ordinary skill in the art to readily determine what is

meant by the phrase "anti-fibrotic agent". Accordingly, Applicants request withdrawal of this rejection.

Claims 8-11 and 13 are objected to under 37 C.F.R. 1.75 as being in improper form as depending from a multiple dependent claim, namely claim 5. Claim 5 has been amended and Applicants submit that the above rejection is rendered moot.

#### **Copending Applications**

As encouraged by the MPEP §2001.06(b), Applicants wish to draw the following copending applications to the Examiner's attention.

U.S. Patent 08/122,508 and U.S. Patent 08/718,492.

In view of the amendments to the claims and the above comments, Applicants submit that the claims are now in condition for allowance. In the event any issues remain in the prosecution of this application, Applicants request that the Examiner call the undersigned attorney to expedite allowance of the claims. If any fees are required for the filing of these papers, Applicants request the Commissioner to charge those fees to deposit account #18-0988.

Respectfully submitted,

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